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(71) Applicant *(for all designated States except US)*: THE BOOTS COMPANY PLC [GB/GB]; 1 Thane Road West, Nottingham NG2 3AA (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : BUSSON, Mervyn [GB/GB]; REES, John, Andrew [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB).

(74) Agent: THACKER, Michael, Anthony; The Boots Company plc, Patents Department, R4 Pennyfoot Street, Nottingham NG2 3AA (GB).

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With international search report.

(54) Title: USE OF 7-FLUORO-1-METHYL-3-METHYLSULPHINYL-4-QUINOLONE IN THE TREATMENT OF ANGINA PECTORIS

(57) Abstract

A method and use are provided for the treatment of angina pectoris in humans, comprising the administration of an effective amount of 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone to a human in need of such treatment. Preferably the active compound is administered in an amount of at least 50 mg, once a day.

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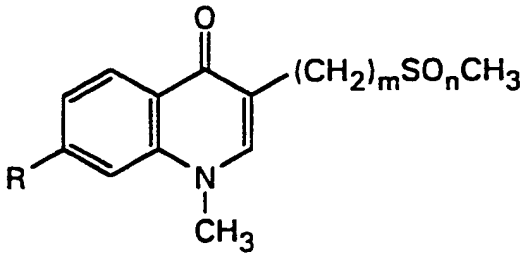
USE OF 7-FLUORO-1-METHYL-3-METHYLSULPHINYL-4-QUINOLONE IN THE TREATMENT OF ANGINA PECTORIS

The present invention relates to a method for the treatment of angina pectoris in humans.

Angina pectoris arises from an imbalance between myocardial oxygen supply and demand. Typically the condition results from narrowing of the coronary arteries through atherosclerosis. This reduces blood flow, and thus oxygen supply, to the heart muscles, resulting in a severe cardiac oxygen deficiency which can cause severe pain to the sufferer. The condition can, in extreme form, be life-threatening. Attacks of angina pectoris are commonly brought on by exercise or by stress which increase oxygen demand in the cardiac muscles to a point where it cannot be met by the reduced supply of blood thereto.

European Patent Publication No. 0149519A (The Boots Company PLC) discloses the use, in the treatment of heart failure, of quinolones of the following general formula (I):

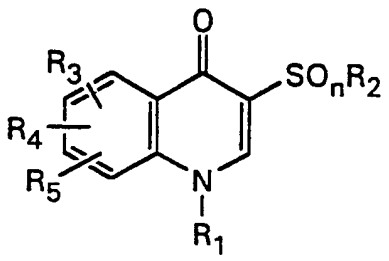


(I)

wherein m is 0 or 1; n is 0, 1 or 2; and R is hydrogen, halo, methyl or trifluoromethyl.

Preferred compounds for such use are stated to be inter alia 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone and 1-methyl-3-methylsulphonyl-methyl-4-quinolone.

British Patent Application No. 8400905, one of two priority documents submitted during prosecution of the above European Patent Application, and thereby laid open to public inspection, discloses quinolones of general formula II



(II)

wherein n is 0, 1 or 2; R_1 is lower alkyl optionally substituted by hydroxy, C_{1-4} alkoxycarbonyl or C_{1-4} alkoxy; allyl; propynyl or phenyl-lower alkyl in which the phenyl ring is optionally substituted by 1 or 2 C_{1-4} alkoxy groups or 1 or 2 C_{1-4} alkyl groups; R_2 is C_{1-4} alkyl, C_{3-4} alkenyl or C_{3-4} alkynyl with the proviso that, when n is 0, R_2 is methyl; and R_3, R_4 and R_5, which may be the same or different, are hydrogen, lower alkyl, lower alkoxy, lower alkanoyl, halo, trifluoromethyl or lower alkylthio.

It is stated in the specification that compounds of formula II are "useful in the treatment of ischaemic heart disease and/or heart failure". It is also stated, later in the specification, that:
"It will be appreciated by those skilled in the art that, in some cases, the patient may have ischaemic heart disease or heart failure but that, in many cases, the patient has both disorders. It will also be appreciated that ischaemic heart disease includes angina and myocardial infarction."

Members of the class of quinolones defined in general formula II are thus disclosed to be of use in the treatment of at least one disorder selected from

ischaemic heart disease and heart failure. The above-mentioned British Patent Application further states that:

"Some of the compounds, for example 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone, also have positive inotropic activity which is an advantage in the treatment of heart failure".

This is reflected in the later-filed European Application (EP-A-0149519) which states (page 7, line 26 to page 8, line 4) that:

" The inotropic activities of 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone and 1-methyl-3-methyl-sulphonylmethyl-4-quinolone were determined by a method similar to that described by Marks, J.E. and Koch-Weser, J. in Journal of Pharmacology and Experimental Therapeutics, 1971, Vol.78, No.1, pp 94-101. Intact left atria from guinea pigs were used in the determinations, and the animals were treated with reserpine, 5 mg/kg given intraperitoneally, 24 hours before removal of the atria. It was found that both compounds have positive inotropic activity. "

This finding is confirmed inter alia by Falotico et al in J. Cardiovasc. Pharmacol. 14, 412-418, where it is reported (page 417) that:

"in electrically stimulated ferret papillary muscle, direct positive inotropic activity is observed with flosequinan and its sulfone derivative in concentrations ranging from 1 to 100μM. This complements hemodynamic studies in anaesthetised dogs ...". Similar results are reported by Greenberg and Touhey in J. Cardiovasc. Pharmacol. 15, 900-1910.

Although thus clearly indicating use in the treatment of heart failure, British Patent Application No. 8400905 makes no specific reference to use of the

particular quinolone 7-fluoro-1-methyl-3-methyl sulphinylmethyl-4-quinolone in treatment of ischaemic heart disease in any form, still less in the particular form known as angina pectoris.

To the contrary, in fact, the disclosure that this particular compound is a positive inotrope teaches the skilled worker away from use in treatment of angina pectoris.

By definition, positive inotropes cause the heart to beat more vigorously, thus increasing oxygen demand from the heart muscles.

As noted above, angina pectoris results inter alia from cardiac oxygen deficiency caused by inadequate blood supply to the heart muscles. Accordingly, by causing the heart to work harder, the administration of a positive inotrope to a patient suffering from angina pectoris would be expected to exacerbate the existing oxygen deficiency by increasing oxygen demand in the very muscles where oxygen supply is scarce, thus causing a deterioration rather than an improvement, in the patient's condition.

7-Fluoro-1-methyl-3-methylsulphinyl-4-quinolone has also been found to have positive chronotropic activity in animals (see, for example, Yates et al, American Heart Journal 1991, 121, pp. 974-983) which could also increase myocardial oxygen demand.

Furthermore, the known vasodilatory action of the present quinolone might cause preferential vasodilation of non-ischaemic coronary vessels, thus diverting blood from diseased ischaemic coronary vessels and further reducing oxygen supply to the affected muscles of the

heart. This effect, known as "coronary steal" might cause further deterioration in the condition of angina.

Surprisingly, however, it has now been found that, despite the positive inotropy and chronotropy previously shown by 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone in animals, this particular compound, when administered to humans suffering from angina, imparts a totally unexpected beneficial effect on the patient's condition.

According to the present invention, there is provided a method for the treatment of angina pectoris in a human in need of such treatment, which comprises the administration to said human of a therapeutically effective amount of 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone.

The term "treatment" includes the therapeutic treatment of a human suffering from angina pectoris and the prophylactic treatment of a human at risk from angina pectoris. Therefore, the invention includes a method of preventing angina pectoris attack in a human susceptible to such attack, by administering to said human an effective amount of 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone.

Preferably, the method of the invention is used in the long term prophylactic management of angina attacks.

The method of the invention may be used in humans who do or do not suffer from heart failure.

As used hereinafter, the term "the active compound" denotes 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone (also known as 'flosequinan'). In man, flosequinan is naturally converted into the corresponding sulphone

compound 7-fluoro-1-methyl-3-methylsulphonyl-4-quinolone by metabolism following administration.

In the method of the present invention, the active compound may be administered enterally or parenterally.

Enteral administration may be oral or rectal. Parenteral administration may be intravenous, intramuscular, or topical. Oral administration is preferred for the treatment of chronic angina, but intravenous administration may be preferred in treating the acute stage of the disease.

In the method of the present invention, the active compound is generally administered in the form of a pharmaceutical composition comprising the active compound together with a pharmaceutically acceptable carrier. Such pharmaceutical compositions may take the form of any of the known pharmaceutical compositions for enteral or parenteral administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention suitably contain 0.1-90% by weight of active compound. The compositions of the invention are often prepared in unit dosage form.

Suitably, the active compound is administered in a dose of at least about 50 mg per day since it has been found that doses below about 50 mg do not always provide the benefit of the invention. Preferably the dose is at least about 75 mg per day, suitably between 75 mg and 150 mg per day, preferably between 75 mg and 125 mg per day, for example about 100 mg per day.

Suitably the active compound is administered as a single dose, once a day. This procedure has the advantage of being convenient to the patient and medical

personnel alike, and minimises the risk that the administration of medication will be overlooked. However, it will be understood that as an alternative, smaller doses could be provided several times a day to provide a total dose of the size described.

Compositions for oral administration are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oily suspensions. The excipients used in the preparation of these compounds are the excipients known in the pharmacist's art. Tablets may be prepared by mixing the active compound with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

Compositions for use in the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Compositions for use in the invention suitable for parenteral administration are the known pharmaceutical forms for such administration, for example, sterile suspensions in aqueous and oily media or sterile solutions in a suitable solvent. Typically such forms might be solutions of glucose or sodium chloride.

Compositions for topical administration may comprise a matrix in which the active compound is dispersed so that the compound can be held in contact with the skin in order to administer the active compound transdermally. Alternatively, the active compound may be dispersed in a cream or ointment base.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example, as obtained by fluid energy milling.

In the compositions of use in the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients, for example, nitrates (such as glyceryl trinitrate, pentaerythritol tetranitrate, isosorbide dinitrate and isosorbide mononitrate), β-blockers (such as acebutolol, atenolol, bisoprolol, metaprolol, carteolol, nadolol, oxprenolol, pinodol, propanolol, sotalol and timolol), calcium antagonists (such as veraprimil, amlodipine, nicardipine, nifedipine and diltiazem) and Angiotensin Converting Enzyme (ACE) inhibitors (such as enalapril, lisinopril and captopril).

Thus, the invention provides a method as defined above, wherein the quinolone is administered simultaneously, sequentially or separately with a therapeutically effective amount of a calcium antagonist, a nitrate compound, or an ACE inhibitor.

There is also provided a product comprising 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone and a calcium antagonist or a nitrate compound, as a combined preparation for simultaneous, sequential or separate administration in the treatment of angina pectoris in humans.

There is further provided a therapeutic composition for the treatment of angina pectoris which comprises a therapeutically effective amount of 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone and a therapeutically effective amount of a calcium antagonist or a nitrate compound.

The present invention also provides the use of 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone in the treatment of angina pectoris in humans.

The invention also provides the use of 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone in the manufacture of a medicament for the treatment of angina pectoris in humans.

Suitably in such uses, the dosage and manner of administration of the active compound are as described above.

It will be appreciated that, in some formulations, the active compound may be present in the form of a therapeutically acceptable acid addition salt thereof.

The following are examples of compositions which may be used in accordance with the method of the present invention.

Composition 1

In the preparation of capsules, 100 parts by weight of 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone and 290 parts by weight of lactose are deaggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing 100 mg of active compound.

Composition 2

In the preparation of capsules, 75 parts by weight of 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone and 325 parts by weight of lactose are deaggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing 75 mg of active compound.

Composition 3

Tablets are prepared from the following ingredients:

	Parts by weight
7-fluoro-1-methyl-3-methyl-sulphinyl-4-quinolone	100
Lactose (spray dried)	74
Microcrystalline cellulose	74
Maize starch	166
Polyvinylpyrrolidone	13
Magnesium stearate	3.5
Methylhydroxypropylcellulose	10
Propylene glycol	1
Titanium dioxide	3

The active compound, lactose, microcrystalline cellulose and maize starch are deaggregated and blended.

The resulting mixture is granulated with a solution of the polyvinylpyrrolidone in denatured ethanol. The dry, sized granulate is blended with the magnesium stearate. The mixture is then compressed in a tabletting machine to give tablets containing 100 mg of flosequinan. The tablets are coated with a mixture of the methylhydroxypropyl cellulose, propylene glycol and titanium dioxide with water and denatured ethanol. All of the titanium dioxide and part of the methylhydroxy propyl cellulose are added as a suspension in denatured ethanol available under the trade name 'Opaspray White'.

Composition 4

Tablets are prepared from the following ingredients:

	Parts by weight
7-fluoro-1-methyl-3-methyl-sulphinyl-4-quinolone	100
Lactose (spray dried)	121
Microcrystalline cellulose	60
Croscarmellose sodium	33
Polyvinylpyrrolidone	13
Magnesium stearate	2.5
Methylhydroxypropyl cellulose	10
Propylene glycol	1
Titanium dioxide Ph Eur E171	3

The active compound, lactose, microcrystalline cellulose and croscarmellose sodium are deaggregated and blended. The resulting mixture is granulated with a solution of the polyvinylpyrrolidone in denatured ethanol. The dry, sized granulate is blended with the magnesium stearate. The mixture is then compressed in a tabletting machine to give tablets containing 100 mg of flosequinan. The tablets are coated with a mixture of the methylhydroxypropyl cellulose, propylene glycol and

titanium dioxide with water and denatured ethanol. All of the titanium dioxide and part of the methylhydroxy propyl cellulose are added as a suspension in denatured ethanol available under the trade name 'Opaspray White'.

Composition 5

Tablets are prepared from the following ingredients:

	Parts by weight
7-fluoro-1-methyl-3-methyl-sulphinyl-4-quinolone	100
Lactose (spray dried)	120
Microcrystalline cellulose	40
Croscarmellose sodium	32
Polyvinylpyrrolidone	13
Magnesium stearate	3
Methylhydroxypropyl cellulose	10
Propylene glycol	1
Titanium dioxide	3

The active compound, lactose, microcrystalline cellulose and croscarmellose sodium are deaggregated and blended. The resulting mixture is granulated with a solution of the polyvinylpyrrolidone in denatured ethanol. The dry, sized granulate is blended with the magnesium stearate. The mixture is then compressed in a tabletting machine to give tablets containing 100 mg of flosequinan. The tablets are coated with a mixture of the methylhydroxypropyl cellulose, propylene glycol and titanium dioxide with water and denatured ethanol. All of the titanium dioxide and part of the methylhydroxy propyl cellulose are added as a suspension in denatured ethanol available under the trade name 'Opaspray White'.

Composition 6

A formulation for intravenous injection is prepared to the following composition:

7 fluoro-1-methyl-3-methyl-sulphinyl-4-quinolone	100 mg
Sodium chloride BP/USP for injections	900 mg
Water for injections to	100 ml

The formulation is sterilised in the course of manufacture.

Composition 7

A formulation for intravenous injection is prepared to the following composition:

7-fluoro-1-methyl-3-methyl-sulphinyl-4-quinolone	100 mg
Glucose BP/USP (pyrogen free)	5.5 g
Water for injections to	100 ml

The formulation is sterilised in the course of manufacture.

The following non-limitative clinical example illustrates the invention.

Clinical Example

A clinical study was carried out in the form of a double-blind placebo controlled crossover trial conducted in two centres in the U.K. Patients fulfilling the entry criteria requiring a diagnosis of chronic, stable angina pectoris of at least three months

duration, without evidence of heart failure, myocardial infarction or stroke in the previous six months were eligible for the study. During a short run in period patients were weaned off any anti-anginal therapy, except emergency nitro-glycerine. They were then randomised to receive 100 mg of flosequinan daily, by oral administration, for seven days followed by a seven day wash out period and then seven days of placebo, or the treatments in the reverse order.

A Bruce Protocol Treadmill Test was used to elicit anginal symptoms and electrocardiographic changes and the times to these end points used as indicators of treatment efficacy. The exercise tests were performed immediately before and one hour after treatment with the trial medications on Day 1 and Day 14 (first day of each of the trial medications = acute response) and on Day 7 and Day 21 (last day of each of the trial medications = chronic response). Adverse events and nitro-glycerine consumption were recorded throughout the trial.

Thirty-seven patients entered and 23 completed the study. Exercise time significantly increased after the first and the seventh dose of flosequinan compared to placebo (38.8 and 48.6 seconds respectively). Flosequinan was also significantly superior to placebo in terms of time to achieve 1mm ST depression and the degree of ST depression after the first dose, the time to achieve maximum ST depression after the first and seventh dose. The remaining ECG parameters and consumption of nitro-glycerine tablets favoured flosequinan but did not achieve statistical significance.

The results from this study demonstrate that flosequinan has an unexpected beneficial effect in angina pectoris.

Claims

1. The use of 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone in the treatment of angina pectoris in humans.

2. The use of 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone in the manufacture of a medicament for the treatment of angina pectoris in humans.

3. A product comprising 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone and a calcium antagonist or a nitrate compound, as a combined preparation for simultaneous sequential or separate administration in the treatment of angina pectoris in humans.

4. A therapeutic composition for the treatment of angina pectoris which comprises a therapeutically effective amount of 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone together with a therapeutically effective amount of a calcium antagonist or a nitrate compound.

5. A method for the treatment of angina pectoris in a human in need of such treatment, which comprises the administration of a therapeutically effective amount of 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone to said human.

6. A method as claimed in claim 5 wherein the treatment comprises preventing angina attack in a human susceptible to such attack.

7. A method as claimed in claim 6 wherein the treatment comprises the long term prophylactic management of angina attacks.

8. A method as claimed in any one of the preceding claims wherein the quinolone is administered enterally.

9. A method as claimed in claim 8 wherein the quinolone is administered orally.

10. A method as claimed in any one of claims 5 to 7 wherein the quinolone is administered parenterally.

11. A method as claimed in claim 10 wherein the quinolone is administered by intravenous injection.

12. A method as claimed in any one of the preceding claims wherein the quinolone is administered at a dose of at least about 50 mg/day.

13. A method as claimed in claim 12 wherein the quinolone is administered at a dose of between 75 mg/day and 150 mg/day.

14. A method as claimed in claim 13 wherein the quinolone is administered at a dose of about 100 mg/day.

15. A method as claimed in any one of the preceding claims wherein the quinolone is administered in a single dose, once a day.

16. A method as claimed in any one of the preceding claims wherein the quinolone is administered simultaneously, sequentially or separately with a therapeutically effective amount of a calcium antagonist, a nitrate compound or an Angiotensin Converting Enzyme (ACE) inhibitor.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/01640

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/47

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	WO,A,9 010 445 (THE BOOTS COMPANY) 20 September 1990 see abstract see page 6, line 32 - page 7, line 4 see page 16, line 1 - line 9	1-16
A	AMERICAN HEART JOURNAL vol. 121, no. 3, 1991, pages 974 - 983 D.B. YATES ET AL. 'PHARMACOLOGY OF FLOSEQUINAN' see the whole document, in particular page 976	1-2,5-16

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° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05 MARCH 1993	23.03.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	HOFF P.J.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	JOURNAL OF CARDIOVASCULAR PHARMACOLOGY vol. 15, no. 6, 1990, pages 900 - 910 S. GREENBERG ET AL. 'POSITIVE INOTROPY CONTRIBUTES TO THE HEMODYNAMIC MECHANISM OF ACTION OF FLOSEQUINAN IN THE INTACT DOG' see the whole document	1-2,5-16
A	CHEMICAL ABSTRACTS, vol. 103, no. 22, 1985, Columbus, Ohio, US; abstract no. 183569e, 'USE OF QUINOLONES FOR TREATING CORONARY INSUFFICIENCY' & DE,A,3 500 756 (BOOTS CO.) 25 July 1985 see abstract	1-2,5-16
A	EP,A,0 149 519 (THE BOOTS COMPANY PLC) 24 July 1985 cited in the application see the whole document	1-2,5-16
A	DRUGS OF THE FUTURE vol. 11, no. 3, 1986, pages 177 - 178 R. MANNHOLD 'BTS-49465' see the whole document	1-2,5-16
X	INTERNATIONAL JOURNAL OF CARDIOLOGY vol. 24, 1989, pages 73 - 76 A. SCHNEEWEISS ET AL. 'THE EFFECT OF FLOSEQUINAN IN PATIENTS WITH HEART FAILURE OF ACUTE ONSET COMPLICATING ACUTE MYOCARDIAL INFARCTION' see the whole document	3-4

International application No.

INTERNATIONAL SEARCH REPORT

PCT/EP 92/01640

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

ALTHOUGH CLAIMS 1,5-16 ARE DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN/ ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9201640
SA 62305

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